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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/824,481	04/15/2004	Vincent Ling	WYS-00501	7025

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EXAMINER	
OUSPENSKI, ILIA I	

ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/824,481	LING ET AL.	
	Examiner	Art Unit	
	ILIA OUSPENSKI	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *3 and 10-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-9 and 17-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/23/04;5/3/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Sequence alignment, 2 pages*.

DETAILED ACTION

1. Applicant's amendment/remarks, filed on 04/09/2007, are acknowledged.

Claims 1 – 21 are pending.

2. Applicant's election with traverse of Group I (claims 1 – 11 and 17 – 21, drawn to a method of inhibiting activation of a lymphocyte comprising contacting the lymphocyte with a soluble form of B7-H3) in the reply filed on 04/09/2007 is acknowledged.

The traversal is on the grounds that allegedly no undue burden would be required to search all inventions.

This is not found persuasive, because, as set forth in the prior office action, the distinct ingredients of the claimed methods require non-coextensive searches, and the methods are classified in different classes and subclasses.

The requirement is still deemed proper and is therefore made FINAL.

Applicant further elected the species wherein the soluble B7-H3 molecules comprise SEQ ID NO:22 or SEQ ID NO:14. Applicant stated that the election of species was made with traverse; however, since applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election of species has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 3 and 10 – 16 are withdrawn from further consideration by the Examiner, under 37 C.F.R. § 1.142(b), as being drawn to nonelected inventions or species, there being no allowable generic or linking claim.

Claims 1 – 2, 4 – 9, and 17 – 21 are under consideration in the instant application.

3 This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reasons set forth herein.

Upon review of the instant application, it is noted that the sequences disclosed at least in Figure 1 *are not accompanied by SEQ ID Numbers*. Applicant is reminded of the sequence rules which require a submission for all sequences of more than 9 nucleotides or 3 amino acids (see 37 CFR 1.821-1.825) and is also requested to carefully review the submitted specification for any and all sequences which require compliance with the rules. Applicant is reminded to amend the specification and the claims accordingly.

Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) in response to this Office Action.

The SEQ ID Numbers for a sequence shown in a drawing may be incorporated in the Brief Description of the drawing.

4. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention *to which the claims are directed.*

5. Claims 17 – 21 are objected to as being dependent on a non-elected claim. It is suggested that Applicant rewrite the claims in independent form to include the limitations of base claims.

6. The following is a quotation of the **second paragraph of 35 U.S.C. 112**.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1 – 2, 4 – 9, and 17 – 21 are rejected under **35 U.S.C. 112, second paragraph**, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 – 2, 4 – 9, and 17 – 21 are indefinite in the recitation of a "B7-H3 agonist," because it is unclear whether the recitation refers to a substance that acts on B7-H3 to activate it, or a substance that mimics the activating action of B7-H3 on its receptor. Therefore, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the claimed invention. For examination purposes, the latter interpretation is presently assumed.

Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

8. The following is a quotation of the **first paragraph of 35 U.S.C. 112**:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1 – 2, 4 – 9, and 17 – 21 are rejected under **35 U.S.C. 112, first paragraph**, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention.

The specification does not enable one of skill in the art to practice the invention as claimed without undue experimentation. Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized in In re Wands (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, limited working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

A. The specification does not provide a sufficient enabling description of a method of inhibiting activation of lymphocytes by contacting the lymphocytes with a "soluble" form of B7-H3.

The instant specification discloses in Examples 4 and 5 that B7-H3 can inhibit activation of lymphocytes when present together with HLA-DR2 on the surface of a cell, or together with anti-CD3 antibody on the surface of a microbead (in cis configuration). At the same time, B7-H3 does not inhibit activation of lymphocytes when present on the surface of microbeads alone, even in the presence of other microbeads carrying anti-CD3 on their surface (trans configuration) (Example 5). Based on this disclosure, one of skill in the art would reasonably conclude that "soluble" B7-H3, i.e. not bound to a surface, and therefore not presented in proximity to either HLA-DR2 or anti-CD3 antibody, would not be able to inhibit activation of lymphocytes.

B. The specification does not provide a sufficient enabling description of a method of inhibiting activation of lymphocytes by contacting the lymphocytes with a generically recited B7-H3 "agonist."

It is noted that the elected invention is limited to a B7-H3 agonist which is a soluble form of B7-H3; however, the present rejection is set forth with regard to the full scope of the generic claims as presently recited.

A person of skill in the art is not enabled to practice the claimed method, because a person of skill in the art is not enabled to make and use any "agonist" of B7-H3 commensurate with the scope of the claims as presently recited, since it was well known in the art at the time the invention was made that molecules having highly diverse structural and biochemical properties can function as "agonists." For example, Huang (Pharmacology and Therapeutics, 2000, 86: 201 – 215; see entire document) reviews e.g. on page 202 the daunting task faced by the skilled artisan in developing small molecule regulators of protein function, and notes that the process requires long periods of trial and error testing. The structure of such molecules cannot be readily determined by one of skill in the art based upon the guidance provided in the specification as-filed. Therefore, Applicant does not provide a sufficiently enabling disclosure regarding how to make and use the generically recited B7-H3 agonists.

C. The specification does not provide a sufficient enabling description of a method of inhibiting activation of lymphocytes in a mammal which is afflicted with cancer or an infectious disease.

One of skill in the art is aware that inhibiting activation of lymphocytes in a cancer or an infectious disease patient would lead to inhibition of the immune response to

cancer cells or the infectious agent, respectively, and therefore would exacerbate rather than improve the patient condition. Therefore, one of skill in the art is not enabled to practice the method as claimed.

D. The specification does not provide a sufficient enabling description of the claimed method, because the specification does not provide a sufficient enabling description of how to make and use a polypeptide comprising an amino acid sequence which is "substantially identical" to the recited sequence, wherein the polypeptide is functional in the claimed methods.

The instant specification defines the phrase "substantially identical" as being at lease 70% identical to the reference sequence (page 18). Therefore, the claims encompass in their breadth a genus of sequences comprising a vast number of diverse variants, while the instant specification discloses only three examples of B7-H3 polypeptides, two human splice variants and one mouse protein.

However, one of skill in the art is aware that even single amino acid differences can result in drastically altered functions of costimulatory proteins. For example, Metzler et al. (Nature Structural Biol. 1997; 4:527-531) show that any of a variety of single amino acid changes can alter or abolish the ability of CTLA4 to interact with its ligands CD80 and CD86 (e.g., summarized in Table 2). Thus it is unpredictable if any functional activity will be shared by two polypeptides having less than 100% identity over the full length of their sequences.

In view of this unpredictability, the skilled artisan would not reasonably expect a generically recited polypeptide "substantially identical" to B7-H3 to share the same function as B7-H3, and there is insufficient guidance to direct the skilled artisan to such functional sequences. Thus the recitation of substantial identity language does not

allow the skilled artisan to make and use the recited polypeptides commensurate in scope with the instant claims without undue experimentation.

10. Claims 1 – 2, 4 – 9, and 17 – 21 are rejected under **35 U.S.C. 112, first paragraph**, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

A. Applicant is not in possession of the claimed method, because Applicant is not in possession of a generically recited B7-H3 "agonist."

It is noted that the elected invention is limited to a B7-H3 agonist which is a soluble form of B7-H3; however, the present rejection is set forth with regard to the full scope of the generic claims as presently recited.

Applicant has not provided a disclosure of sufficiently detailed, relevant identifying characteristics, such as complete or partial structure, or functional characteristics when coupled with a known or disclosed correlation between function and structure, to describe the recited genus. It was well known in the art at the time the invention was made that molecules having highly diverse structural and biochemical properties can function as "agonists." For example, Huang (Pharmacology and Therapeutics, 2000, 86: 201 – 215; see entire document) reviews e.g. on page 202 the daunting task faced by the skilled artisan in developing small molecule regulators of protein function, and notes that the process requires long periods of trial and error testing. The structure of such molecules cannot be readily envisioned by one of skill in the art based upon the written description provided in the specification as-filed.

B. Applicant is not in possession of the claimed method, because Applicant is not in possession of a polypeptide comprising an amino acid sequence which is "substantially identical" to the recited sequence, wherein the polypeptide is functional in the claimed methods.

The instant specification defines the phrase "substantially identical" as being at lease 70% identical to the reference sequence (page 18). Therefore, the claims encompass in their breadth a genus of sequences comprising a vast number of diverse variants, while the instant specification discloses only three examples of B7-H3 polypeptides, two human splice variants and one mouse protein.

However, one of skill in the art is aware that even single amino acid differences can result in drastically altered functions of costimulatory proteins. For example, Metzler et al. (Nature Structural Biol. 1997; 4:527-531) show that any of a variety of single amino acid changes can alter or abolish the ability of CTLA4 to interact with its ligands CD80 and CD86 (e.g., summarized in Table 2). Thus in the absence of sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, the claimed invention is not described in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

A description of a genus of protein sequences may be achieved by means of a recitation of a representative number of polypeptide sequences, defined by amino acid sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. Regents of the University of California v. Eli Lilly&Co., 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111. makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, January 5, 2001.

11. The following is a quotation of the appropriate paragraphs of **35 U.S.C. 102** that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

12. Claims 1 – 2, 4 – 9, and 17 – 20 are rejected under **35 U.S.C. 102(a) and 102(e)** as being anticipated by Mikesell et al. (US Pat. Pub. No. 2002/0095024; see entire document).

Mikesell et al. teach and claim a method for decreasing (inhibiting) lymphocyte activity in a subject, comprising administering to the subject a polypeptide comprising amino acid sequence of SEQ ID NO:7 or SEQ ID NO:13 (e.g. claim 28).

The instantly recited SEQ ID NO:22 is identical to amino acids 246 – 357 of SEQ ID NO:7 (BSL2-4616811 polypeptide) taught by Mikesell et al., while instantly recited SEQ ID NO:14 is identical to amino acids 28 – 139 of SEQ ID NO:13 taught by Mikesell et al., as shown in the attached alignments.

Mikesell et al. further teach a method wherein tissue culture plates are coated with anti-CD3 antibody (a primary stimulatory molecule) followed by addition of BSL2-4616811-Ig fusion protein (e.g. paragraphs 0328 – 0330), which therefore becomes couples with the primary stimulatory molecule. The plates are used for incubation of T cells, which are thus contacted with both agents.

Mikesell et al. also teach that the proteins of the invention can be administered to treat immune disorders, infections, or cancer (e.g. paragraphs 0177 – 0178 and 0194 – 0195).

Therefore, the reference teachings anticipate the instant claimed invention.

13. Conclusion: no claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILIA OUSPENSKI whose telephone number is 571-272-2920. The examiner can normally be reached on Monday-Friday 9 - 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ilia Ouspenski

ILIA OUSPENSKI, Ph.D.
Patent Examiner
Art Unit 1644

June 19, 2007